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EXAMINER	
HUYNH, PHUONG N	

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 10/019,501	Applicant(s) OGATA ET AL.	
	Examiner Phuong Huynh	Art Unit 1644	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *Three* MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *20 October 2004*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1 and 4-25* is/are pending in the application.

4a) Of the above claim(s) *12-22* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1, 4-5, 7-11, and 23-25* is/are rejected.

7)☒ Claim(s) *6* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

1. Claims 1 and 4-25 are pending.

2. Claims 12-22 stand withdrawn from further consideration by the examiner, 37 C.F.R. 1.142(b) as being drawn to non-elected inventions.

3. Claims 1, 4-11, and 23-25 are being acted in this Office Action.

4. In view of the amendment filed 10/20/04, the following rejections remain.

5. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

6. Claims 1, 4-5, 7-11, and 23-25 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor, at the time the application was filed, had possession of the claimed invention.

The specification does not reasonably provide a **written description** for antibody such as monoclonal, humanized, chimeric, antibody fragment and modified form of said fragment that binds to *all* "PTHrP" and *any* part of PTHrP other than N-terminal 1-34 of human PTHrP as a method of maintaining or increasing low vasopressin level or a method of treating at least one symptom caused by a decrease in vasopressin level.

The specification discloses only human PTHrP and various methods of making antibody that binds specifically to the N terminal 1-34 of human PTHrP consisting of SEQ ID NO: 75.

With the exception of the specific antibody mentioned above that binds specifically to the N-terminal of human PTHrP1-34 consisting of the amino acid sequence of SEQ ID NO: 75, there is insufficient written description about the structure associated with function without the amino acid sequence of *all* PTHrP to which the antibody binds for the claimed method. Other than N-terminal of human PTHrP1-34 to which the antibody binds for the claimed method, the binding specificity of the antibody to other part of PTHrP1-34 other than terminal of human PTHrP1-34

in the claimed method is not adequately described. Given the lack of any additional parathyroid hormone related peptide (PTHrP) and C terminal part of PTHrP to which the antibody binds in the claimed method, one of skill in the art would reasonably conclude that the disclosure fails to provide a representative number of species to describe the genus. Thus, Applicant was not in possession of the claimed genus. *See University of California v. Eli Lilly and Co. 43 USPQ2d 1398.*

Applicant is directed to the Final Guidelines for the Examination of Patent Applications Under the 35 U.S.C. 112, ¶ 1 "Written Description" Requirement, Federal Register, Vol. 66, No. 4, pages 1099-1111, Friday January 5, 2001.

Applicants' arguments filed 10/20/04 have been fully considered but are not found persuasive. Applicants' position is that that the structure of full-length PTHrP was known in the art at the time the application was filed. Further, the specification contains an actual reduction to practice of the claimed invention, which demonstrates that an anti-PTHrP antibody maintains or increases vasopressin level in an animal model of hypercalcemia. See specification at pages 19-24.

In response, the specification discloses only a method of maintaining or increasing low vasopressin level comprising administering to a patient only antibody such as monoclonal antibody produced by hybridoma #23-57-154, #23-57-137-1, humanized, chimeric and antibody binding fragment thereof that binds specifically to human PTHrP. The specification discloses only *human* PTHrP and method of making antibody that binds to human PTHrP using the N terminal 1-34 amino acids of human PTHrP. Other than human PTHrP to which the antibody binds for the claimed method, the rest of the PTHrP and the binding specificity of the antibody in the claimed method are not adequately described.

Given the lack of any additional parathyroid hormone related peptide (PTHrP) to which the antibody binds in the claimed method, one of skill in the art would reasonably conclude that the disclosure fails to provide a representative number of species to describe the genus. Thus, Applicant was not in possession of the claimed genus. *See University of California v. Eli Lilly and Co. 43 USPQ2d 1398.*

7. The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter, which the applicant regards as his invention.

8. Claims 1 and 4 stand rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The "fragment of anti-PTHrP antibody" in claim 4 is ambiguous and indefinite because antibody has the antigen binding fragment and the Fc fragment and it is not clear which fragment of the antibody applicant intends to claim. In addition to the problem with the fragment, it is not clear which "modified form of the fragment" that is part of the claimed invention. One of ordinary skill in the art cannot appraise the metes and bound of the claimed invention.

Applicants' arguments filed 10/20/04 have been fully considered but are not found persuasive.

Applicants' position is that at page 12, lines 21-23 of the specification a fragment is defined as "Fab, F(ab')2 Fv, or a single chain (scFv) composed of a H-chain Fv fragment and a L-chain Fv fragment linked together through a suitable linker.

In response, it is suggested that claim 4 be amended to recite "...an antibody binding fragment ...". Further, it is suggested that claim 1 be amended to provide antecedent basis for "antibody binding fragment" for claim 4. For example, "...anti-PTHrP antibody or binding fragment thereof that inhibits...".

9. The following new grounds of rejections are necessitated by the amendment filed 10/20/04.

10. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

11. Claims 1, 4-5, 7-11, and 23-25 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling only for a method of maintaining or increasing low vasopressin level comprising administering to a patient only antibody or antigen antibody binding fragment thereof that binds specifically to the N-terminal 1-34 of human PTHrP consisting of SEQ ID NO: 75, **does not** reasonably provide enablement for a method as set forth in claims 1, 4-5, 7-11 and 23-25. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in **scope** with these claims.

Factors to be considered in determining whether undue experimentation is required to practice the claimed invention are summarized *In re Wands* (858 F2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988)). The factors most relevant to this rejection are the scope of the claim, the amount of direction or guidance provided, the lack of sufficient working examples, the unpredictability in the art and the amount of experimentation required to enable one of skill in the art to practice the claimed invention. The specification disclosure is insufficient to enable one skilled in the art to practice the invention as broadly claimed without an undue amount of experimentation.

The specification discloses only human PTHrP and method of making antibody that binds specifically to the N terminal 1-34 of human PTHrP consisting of SEQ ID NO: 75.

The specification does not teach how to make antibody such as monoclonal, humanized, chimeric, antibody fragment and modified form of said fragment that binds to *all* "PTHrP". The specification does not teach antibody such as monoclonal, humanized, chimeric, antibody fragment and modified form of said fragment that binds to the other part of PTHrP such as C-terminal part of all PTHrP, is effective for inhibiting binding between PTHrP and a receptor thereof, in turn, would be useful as a method of maintaining or increasing low vasopressin level or a method of treating at least one symptom caused by a decrease in vasopressin level.

Stryer *et al*, of record, teach that a protein is highly dependent on the overall structure of the protein itself and that the primary amino acid sequence determines the conformational of the protein (See enclosed appropriate pages).

Ngo *et al*, of record, teach that the amino acid positions within the polypeptide/protein that can tolerate change such as conservative substitution or no substitution, addition or deletion which are critical to maintain the protein's structure/function will require guidance (See Ngo et al., 1994, The Protein Folding Problem and Tertiary Structure Prediction, pp. 492-495).

It has been well known to those skilled in the art at the time the invention was made that minor structural differences in the antigen would change the binding specificity of the antibody. Kuby *et al*, of record, teach that antibody epitopes (B cell epitopes) are not linear and are comprised of complex three-dimensional array of scattered residues which will fold into specific conformation that contribute to binding (See Kuby 1994, page 94, in particular). Immunization with a peptide fragment derived from a full-length polypeptide may result in **antibody specificity** that differs from the antibody specificity directed against the native full-length polypeptide. There is insufficient guidance as to which antigen such as PTHrP would produce antibody that

binds to specifically to human PTHrP, in turn, would be useful for a method of maintaining low vasopressin level and which PTHrP antigen would produce antibody that would increase low vasopressin level.

Abaza *et al* teach that even a single amino acid substitution outside the antigenic site can exert drastic effects on the reactivity of a protein with monoclonal antibody against the site (See abstract, in particular). Further, the specification discloses only monoclonal antibody that binds to human PTHrP (1-34) consisting of SEQ ID NO: 75, the binding specificity of other monoclonal antibody, fragment thereof, chimeric and humanized antibody are not enabled.

Since the binding specificity of the antibody in the claimed methods is not enabled, it follows that any monoclonal antibody, any antibody fragment instead of the binding fragment, chimeric antibody, and humanized antibody that bind to *all* PTHrP for the claimed methods are not enabled.

For these reasons, it would require undue experimentation of one skilled in the art to practice the claimed invention. See page 1338, footnote 7 of Ex parte Aggarwal, 23 USPQ2d 1334 (PTO Bd. Pat App. & Inter. 1992).

In re wands, 858 F.2d at 737, 8 USPQ2d at 1404 (Fed. Cir. 1988), the decision of the court indicates that the more unpredictable the area is, the more specific enablement is necessary. In view of the quantity of experimentation necessary, the limited working examples, the unpredictability of the art, the lack of sufficient guidance in the specification and the breadth of the claims, it would take an undue amount of experimentation for one skilled in the art to practice the claimed invention.

Applicants' arguments filed 10/20/04 have been fully considered but are not found persuasive.

Applicants' position is that claims have been amended. One of skill in the ad would be able to make and use the claimed invention, as amended, using the following teachings in the application as a guide: A description of antibodies and methods of making them is provided on pages 4-5 of the specification. A specific example of an antibody, #23-57-137-1, is also provided along with information regarding its deposit under Accession No. FERM BP-5631. The specification at pages 5-8 teaches how a monoclonal antibody-producing hybridoma can be prepared. The production of recombinant antibodies is taught at pages 8-10. The preparation of modified antibodies and fragments of antibodies is discussed at pages 12-14. Expression, production, isolation, and purification of recombinant or modified antibodies are detailed at pages

14-16. Determination of the binding activity and neutralizing activity of an antibody is taught at page 16.

In response, the specification discloses only a method of maintaining or increasing low vasopressin level comprising administering to a patient only antibody such as monoclonal antibody produced by hybridoma #23-57-154, #23-57-137-1, humanized, chimeric and antibody binding fragment thereof that binds specifically to *human* PTHrP. The specification discloses only human PTHrP and method of making antibody that binds to human PTHrP using the N terminal 1-34 amino acids of human PTHrP. The specification does not teach how to make antibody such as monoclonal, humanized, chimeric, antibody fragment and modified form of said fragment that binds to *all* "PTHrP" as a method of maintaining or increasing low vasopressin level or a method of treating at least one symptom caused by a decrease in vasopressin level.

12. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 103(a) that form the basis for the rejections under this section made in this Office Action:

A person shall be entitled to a patent unless:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

13. This application currently names joint inventors. In considering Patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

14. Claims 1, 4, 7-11 and 25 are rejected under 35 U.S.C. 103(a) as being unpatentable over Yamamoto *et al* (Endocrinology 138(1): 383-388; PTO 892) in view of Sato *et al* (J Bone Miner Res 8(7): 849-60, 1993; PTO 1449), Harlow *et al* (in Antibodies a Laboratory Manual, 1988, Cold Spring harbor laboratory publication, Cold Spring Harobr, NY, pages 626-629) and Hotta et al (Endocr J 45(6): 773-8, Dec 1998; PTO 892).

Yamamoto *et al* teach a method of increasing low vasopressin level in a patient such as rat by administering to said patient at least one substance such as PTHrP(1-34) fragment (See Fig 1, in particular). The reference PTHrP inherently competes and thereby inhibiting the binding of the full length PTHrP to a receptor such as PTHrP receptor and PTH receptor and thereby increasing the vasopressin level (See page 387, column 2, third paragraph, in particular). The reference further teaches a method of maintaining vasopressin level by administering to the patient a substance such as a competitive antagonist to PTHrP such as PTHrP(7-34) (See Fig 2, page 387, column 2, last paragraph, in particular). The reference further teaches that arginine-vasopressin (AVP) has anti-diuretic and pressor activity and is produced from hypothalamic magnocellular neurons in the suproptic nucleic (SON) and paraventricular nuclei of the brain (See page 383, column 2, second paragraph, in particular). Yamamoto et al further teach that centrally administered (icv) causes the secretion of AVP from the thalamus and the plasma AVP levels is similar to the levels observed after the restriction of water and food intake or hyperosmolarity induced by i.p. injection of hyperosmotic saline (See page 387, column 2, second paragraph, in particular).

The claimed invention in claim 1 differs from the teachings of the reference only that the method of maintaining or increasing low vasopressin level comprises administering to a patient at least one anti-PTHrP antibody that inhibits the binding between PTHrP and a receptor thereof.

The claimed invention in claim 4 differs from the teachings of the reference only that the method wherein the antibody is at least one of a fragment of an anti-PTHrP antibody.

The claimed invention in claim 7 differs from the teachings of the reference only that the method wherein the substance is a monoclonal anti-PTHrP antibody.

The claimed invention in claim 8 differs from the teachings of the reference only that the method wherein the low vasopressin level results from cancer.

The claimed invention in claim 25 differs from the teachings of the reference only that the method wherein the antibody is Fab or F(ab)2.

Sato *et al* teach malignancy associated hypercalcemia is mainly caused by excessive production of parathyroid hormone related protein (PTHrP) by tumor (See abstract, in particular). The symptoms of excess PTHrP include hypercalcemia, cachexia that is associated with polyuria, dehydration and hyperosmolarity due to hypercalcemia, and increasing osteoclastic bone resorption (See 849, in particular). Sato *et al* teach daily SC injection of anti-PTHrP 1-34 monoclonal antibody which inhibiting the binding between PTHrP and its receptor led to a

decrease in serum calcium, increase in body weight and survival of nude mice bearing PTHrP producing tumors (See abstract, in particular). Sato et al teach that if a human monoclonal antibody against PTHrP(1-34) could be develop, then passive immunization would be potentially one of the most effective therapies associated with hypercalcemia due to excessive production of PTHrP.

Harlow et al teach a method of producing antibody fragment such as Fab fragment or F(ab)2 (See page 626-629, in particular). Harlow *et al* further teach that the problems of using multivalent antibodies on mammalian cells often will lead to capping and internalization of the antigen which can be overcome by using fragments of antibodies (See page 626 in particular).

Hotta et al teach hypercalcemia in euthyroid patient with secondary hypoadranalism and diabetes insipidus due to hypothalamic tumor is associated with decrease in arginine vasopressin and symptoms caused by a decrease in vasopressin level includes polyuria, severe dehydration, disturbance of thirst sensation caused by the hypothalamic tumor (See abstract, in particular).

Therefore, it would have been obvious to one of ordinary skill in the art at the time the invention was made to substitute the PTHrP(1-34) fragment that inhibits the binding between PTHrP and a receptor as taught by Yamamoto et al for the monoclonal antibody that binds to PTHrP(1-34) as taught by Sato et al or PTHrP(1-34) or antibody fragment such as Fab or F(ab)2 produced by the method as taught by Harlow et al for a method of maintaining or increasing low vasopressin level as taught by Yamamoto et al and Sato et al to treat symptoms associated with increased hypercalcemia and decrease in vasopressin level as taught by Hotta et al. From the combined teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention.

One having ordinary skill in the art would have been motivated to do this because Yamamoto et al teach that centrally administered (icv) PTHrP (1-34) causes the secretion of AVP from the thalamus and the plasma AVP levels is similar to the levels observed after the restriction of water and food intake or hyperosmolarity induced by i.p injection of hyperosmotic saline (See page 387, column 2, second paragraph, in particular). Sato *et al* teach malignancy associated hypercalcemia is mainly caused by excessive production of parathyroid hormone related protein (PTHrP) by tumor (See abstract, in particular) and monoclonal antibody to PTHrP (1-34) inhibits the binding between PTHrP and its receptor led to a decrease in serum calcium, increase in body weight and survival of nude mice bearing PTHrP producing tumors (See abstract, in particular). Hotta et al teach hypercalcemia in euthyroid patient with secondary hypoadranalism and diabetes

insipidus due to hypothalamic tumor is associated with arginine vasopressin and symptoms caused by a decrease in vasopressin level includes polyuria, severe dehydration, disturbance of thirst sensation caused by the hypothalamic tumor (See abstract, in particular). Harlow *et al* further teach that the problems of using multivalent antibodies on mammalian cells often will lead to capping and internalization of the antigen which can be overcome by using fragments of antibodies (See page 626 in particular).

Applicants' arguments filed 10/20/04 have been fully considered but are not found persuasive.

Applicants' position is that the cited references do not teach or suggest all claim limitations. Yamamoto et al. does not teach or suggest the use of a PTHrP fragment as a competitive inhibitor of binding of the full length PTHrP protein to the previously described type I or type 11 receptors. The Yamamoto et al. reference refers to a distinct effect of the PTHrP(1-34) fragment, which is unrelated to the binding of full length PTHrP to the type I and type 11 receptors. Given the fact that Yamamoto et al. fully describes the mechanism of action of the PTHrP(1-34) fragment, even if the novel receptor is not fully characterized, Applicants assert that the Office's statement that the PTHrP(1-34) fragment is a competitive inhibitor of the binding of the full length PTHrP protein to a type I or type II receptor is not supported by the record. Furthermore, Sato et al does not teach or suggest maintaining or increasing vasopressin levels using an anti-PTHrP antibody. As the Examiner states, Sato et al. teach that a "monoclonal antibody to PTHrP (1-34) inhibits the binding between PTHrP and its receptor I and) led to a decrease in serum calcium, increase in body weight and survival of nude mice bearing PTHrP producing tumors." Office Action at page 10. The reference does not discuss vasopressin levels, nor the effect of PTHrP/PTHrP receptor binding on such levels. Thus, Yamamoto et al. and Sato el a/., taken together, do not teach or suggest increasing or maintaining vasopressin level by administering an antibody that inhibits the binding between PTHrP and a receptor thereof.

In response to applicant's argument Sato et al does not teach or suggest maintaining or increasing vasopressin levels using an anti-PTHrP antibody, if Sato et al teach or suggest maintaining or increasing vasopressin levels using an anti-PTHrP antibody, the rejection would have been under 35 U.S.C. 102(b). In response to applicant's argument that Yamamoto et al. does not teach or suggest the use of a PTHrP fragment as a competitive inhibitor of binding of the full length PTHrP protein to the previously described type I or type II receptors, Yamamoto *et al* teach a method of increasing low vasopressin level in a patient such as rat by administering to

said patient at least one substance such as PTHrP(1-34) fragment (See Fig 1, in particular). The binding of the reference PTHrP (1-34) fragment to which type I or type II receptors is irrelevant since none of the claims recite the particular type I or type II receptors.

15. Claim 5 is rejected under 35 U.S.C. 103(a) as being unpatentable over Yamamoto *et al* (Endocrinology 138(1): 383-388; PTO 892) in view of Sato *et al* (J Bone Miner Res 8(7): 849-60, 1993; PTO 1449), Harlow *et al* (in Antibodies a Laboratory Manual, 1988, Cold Spring harbor laboratory publication, Cold Spring Harbor, NY, pages 626-629) and Hotta *et al* (Endocr J 45(6): 773-8, Dec 1998; PTO 892) as applied to claims 1, 4, 7-11 and 25 mentioned above and further in view of US Pat No. 6,180,370B (filed June 1995; PTO 892).

The combined teachings of Yamamoto *et al*, Sato *et al*, Harlow *et al* and Hotta *et al* have been discussed supra.

The claimed invention in claim 5 differs from the combined teachings of the references only in that the method wherein the antibody is a humanized or chimeric antibody.

The '370 patent teaches a method of producing chimeric antibodies (See column 55 lines 25-59; column 59, lines 65, in particular) and humanized antibodies (See column 44 line 33; column 68 lines 8-44, in particular). The '370 patent further teaches that humanized immunoglobulin (antibodies) specifically reactive with strong affinity to a predetermined antigen and remain nonimmunogenic in humans and yet be easily and economically produced in a manner suitable for therapeutic formulation and other uses (See column 2, lines 29-34, in particular).

Therefore, it would be been obvious to one having ordinary skill in the art at the time the invention was made to produce humanized or chimeric antibody as taught by the '370 patent using the monoclonal antibody that binds specifically to PTHrP as taught by Sato et al or Harlow et al for a method of maintaining or increasing low vasopressin level as taught by Yamamoto et al and Sato et al or to treat symptoms associated with increased hypercalcemia and decrease in vasopressin level as taught by Hotta et al. From the combined teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention.

One having ordinary skill in the art at the time the invention was made would have been motivated with an expectation of success to produce chimeric or humanized antibodies because the '370 patent teaches that the chimeric humanized immunoglobulin (antibodies) specifically

reactive with strong affinity to a predetermined antigen and remain nonimmunogenic in humans yet be easily and economically produced in a manner suitable for therapeutic formulation and other uses (See column 2, lines 29-34, in particular). Sato et al teach that if a human monoclonal antibody against PTHrP(1-34) could be develop, then passive immunization would be potentially one of the most effective therapies associated with hypercalcemia due to excessive production of PTHrP.

16. Claims 23-24 are rejected under 35 U.S.C. 103(a) as being unpatentable over Yamamoto *et al* (Endocrinology 138(1): 383-388; PTO 892) in view of Sato *et al* (J Bone Miner Res 8(7): 849-60, 1993; PTO 1449), Harlow *et al* (in Antibodies a Laboratory Manual, 1988, Cold Spring harbor laboratory publication, Cold Spring Harbor, NY, pages 626-629) and Hotta *et al* (Endocr J 45(6): 773-8, Dec 1998; PTO 892) as applied to claims 1, 4, 7-11 and 25 mentioned above and further in view of Kitamura et al (Biochem Biophys Res Commun 171(3): 1387-94, Sept 1990; PTO 892).

The combined teachings of Yamamoto *et al*, Sato *et al*, Harlow *et al* and Hotta *et al* have been discussed supra.

The claimed invention in claim 23 differs from the combined teachings of the references only in that the method wherein the antibody fragment is bound to a carrier.

The claimed invention in claim 24 differs from the combined teachings of the references only in that the method wherein the antibody fragment is bound to a PEG.

Kitamura et al teach a method of conjugating antibody fragment such as F(ab')2 to a carrier such as polyethylene glycol (PEG) (see entire document, abstract, in particular). Kitamura et al teach that PEG-conjugated antibody fragment could be a promising carrier for use in targeting cancer chemotherapy because PEG-conjugated antibody fragment retains its antigen-binding activity, improves half life of the antibody fragment and increased accumulation in tumors (see abstract, in a particular).

Therefore, it would be been obvious to one having ordinary skill in the art at the time the invention was made to substitute the F(ab)2 that bound to a carrier such as PEG as taught by Kitamura for the Fab or F(ab)2 fragment that binds to PTHrP as taught by Harlow at al and Sato *et al* for a method of maintaining or increasing low vasopressin level as taught by Yamamoto et al and Sato et al or to treat symptoms associated with increased hypercalcemia and decrease in vasopressin level as taught by Hotta et al. From the combined teachings of the references, it is

apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention.

One having ordinary skill in the art at the time the invention was made would have been motivated with an expectation of success to produce antibody fragment bound to a carrier such as PEG because Kitamura et al teach that PEG-conjugated antibody fragment could be a promising carrier for use in targeting cancer chemotherapy since PEG-conjugated antibody fragment retains its antigen-binding activity, improves half life of the antibody fragment and increased accumulation in tumors (see abstract, in a particular).

17. Claim 25 is rejected under 35 U.S.C. 103(a) as being unpatentable over Yamamoto *et al* (Endocrinology 138(1): 383-388; PTO 892) in view of Sato *et al* (J Bone Miner Res 8(7): 849-60, 1993; PTO 1449), Harlow *et al* (in Antibodies a Laboratory Manual, 1988, Cold Spring harbor laboratory publication, Cold Spring Harobr, NY, pages 626-629) and Hotta *et al* (Endocr J 45(6): 773-8, Dec 1998; PTO 892) as applied to claims 1, 4, 7-11 and 25 mentioned above and further in view of US Pat No. 4,946,778 (Aug 1990, PTO 892).

The combined teachings of Yamamoto *et al*, Sato *et al*, Harlow *et al* and Hotta *et al* have been discussed supra.

The claimed invention in claim 25 differs from the combined teachings of the references only in that the method wherein the antibody fragment is scFv or Fv.

The '778 patent teaches a method of producing single chain antibody comprising a variable region of any antibody (See column 29, lines 25 bridging column 30, lines 1-20, in particular). The advantages of a single chain antibody are small size, greater stability, significantly reduced cost and could be engineered to be highly antigenic and yet reduce the body's immunologic reaction and thus increase the safety and efficacy of the therapeutic application (See column 3, lines 33-48, in particular).

Therefore, it would be been obvious to one having ordinary skill in the art at the time the invention was made with an expectation of success to make single chain antibody as taught by the '778 patent using the antibody that binds to PTHrP as taught by Sato *et al* or antibody fragments as taught by Sato et al and Harlow et al for a method of maintaining or increasing low vasopressin level as taught by Yamamoto et al and Sato et al or to treat symptoms associated with increased hypercalcemia and decrease in vasopressin level as taught by Hotta et al. From the combined

teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention.
One having ordinary skill in the art at the time the invention was made would have been motivated with an expectation of success to produce

One having ordinary skill in the art at the time the invention was made would have been motivated to do this because the '778 patent teaches the advantages of a single chain antibody are small size, greater stability, significantly reduced cost and could be engineered to be highly antigenic and yet reduce the body's immunologic reaction and thus increase the safety and efficacy of the therapeutic application (See column 3, lines 33-48, in particular).

18. Claim 6 is objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims.

19. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, THIS ACTION IS MADE FINAL. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

20. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Phuong Huynh "NEON" whose telephone number is (571) 272-0846. The examiner can normally be reached Monday through Friday from 9:00 am to 5:30 p.m. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christina Chan can be reached on (571) 272-0841. The IFW official Fax number is (571) 273-8300.

21. Any information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

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January 7, 2005

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